Emerging Infections

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Emerging/Re-Emerging Infections

• New, previously unknown infectious agent and disease

• Previously described infectious agent presenting
  – In a new geographic location
  – As a new syndrome
  – In a new type of host
  – With an increased drug resistance pattern or other new genetic characteristic (that changes host range or pathogenicity)

• New or previously described infectious agents used as bioweapons
Selected Emerging/Re-Emerging Infections in Past 30+ Years

- HIV/AIDS
- HTLV-I and II
- HHV 6 and 8
- Hantavirus pulmonary syndrome
- West Nile virus
- Ebola virus
- Nipah/Hendra viruses
- GB virus C
- Transfusion-transmitted virus (TTV)
- SARS
- Monkeypox
- Avian influenza virus
- H1N1 pandemic influenza virus
- Bovine spongiform encephalopathy (vCJD)
- Legionnaire’s disease
- Lyme disease
- Toxic-shock syndrome
- Ehrlichiosis
- Escherichia coli 0157:H7
- Helicobacter pylori
- Tuberculosis, esp. multidrug & extremely drug resistant (MDR & XDR) TB
- Vancomycin resistant enterococci
- Vancomycin intermediate/resistant Staph. aureus
- Community-associated Staph. aureus
- Clostridium difficile colitis
- Use of anthrax as a bioweapon

Emerging/Re-Emerging Infections: Why?

- Ecologic changes
  - Agriculture
  - Flood/drought/climate change
  - Famine

- Human demographics, behavior
  - Population growth and migration
  - War or civil conflict
  - Urban decay
  - Sexual behavior/injection drug use

- International travel and commerce
  - Worldwide movement of goods and people

Adapted from Morse SS: Emerg Infect Dis 1995;1:7-15
Emerging/Re-Emerging Infections: Why?

- Technology and industry
  - Globalization of food supplies
  - Organ/tissue transplantation
  - Immunosuppressive drugs
  - Widespread antibiotic use

- Microbial adaptation and change
  - Microbial evolution
  - Response to selection in environment

- Breakdown in public health measures
  - Curtailment or reduction in prevention programs
  - Inadequate sanitation and vector control measures

- Advances in basic science research
  - Improved cultivation/detection/characterization of micro-organisms

Adapted from Morse SS: Emerg Infect Dis 1995;1:7-15

Emerging Infectious Diseases: Examples

- HIV/AIDS

- Hantavirus pulmonary syndrome

- Avian influenza

- Variant Creutzfeldt-Jakob disease (vCJD) (Bovine spongiform encephalopathy)
HIV/AIDS

New Agent and Disease

First Clinical Description of AIDS:

In the period October 1980–May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

MMWR 1981;30:250-252
Follow-Up: First 26 Cases of Kaposi’s Sarcoma

Kaposi’s Sarcoma and Pneumocystis Pneumonia Among Homosexual Men — New York City and California

During the past 30 months, Kaposi’s sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

MMWR 1981:30:306-308

Follow-Up: First 108 Cases

Follow-Up on Kaposi’s Sarcoma and Pneumocystis Pneumonia

Twenty-six cases of Kaposi’s sarcoma (KS) and 15 cases of Pneumocystis carinii pneumonia (PCP) among previously healthy homosexual men were recently reported (1,2). Since July 3, 1981, CDC has received reports of an additional 70 cases of these 2 conditions in persons without known underlying disease. The sex, race, sexual preference, and mortality data known for 108 persons with either or both conditions are summarized in Table 1.

MMWR 1981:30:409-410
### Early Events in the AIDS Epidemic

- 1981 – Clusters of cases of *Pneumocystis carinii* (now *jirovici*) pneumonia and Kaposi’s sarcoma in gay men reported
- 1981-83 – Opportunistic infections reported in hemophiliacs, injection drug users and transfusion recipients
- 1983 – Virus isolated in tissue culture
  - HTLV-III, LAI – later renamed as HIV-1
- 1985 – Blood screening test became commercially available

### Early Questions in AIDS Epidemic

- Was this one disease or multiple diseases?
- Was this due to a known or unknown pathogen or toxin?
- If infectious, what type of agents was it and how was it transmitted?
- What steps could be taken to protect individual and public health prior to identification of the etiologic agent?
Postulated Causes of AIDS

- **Known viruses**
  - e.g., cytomegalovirus or Epstein-Barr virus

- **Toxic recreational drug exposure**
  - Amyl nitrite

- **New pathogen**

Scientific Progress Which Facilitated the Discovery of HIV-1

- Identification of T-cell growth factor (IL-2) permitting in vitro culture of PBMC’s

- Identification of T cell subsets and surface markers characterizing helper (CD4) and suppressor (CD8) cells

- Identification of human retroviruses
  - HTLV-1 and HTLV-2
Search for Causality in AIDS

- Clinical observations

- Available data
  - Ecologic studies suggested 4 high risk groups
    - MSM, IDUs, hemophiliacs, Haitians
      - Latter illustrates potential to be misled and damage it can cause

- Case-control and cohort studies
  - Individual risks began to be identified but key was isolation of HIV in culture

- Randomized trials
  - Specific anti-HIV treatment and prophylaxis trials provided additional evidence of causality

Estimated Number of AIDS Cases and Deaths among Adults and Adolescents with AIDS, 1985–2005—United States and Dependent Areas

- AIDS
- Deaths

Note: Data have been adjusted for reporting delays.

Revised June 2007
Evidence for a Causal Relationship for Infectious Diseases
Henle and Koch’s Postulates

- The organism is always found with the disease
- The organism is not found with any other disease
- The organism, isolated from one who has the disease, and cultured through several generations, produces the disease (in experimental animals)
- Even when an infectious disease cannot be transmitted to animals, the ‘regular’ and ‘exclusive’ presence of the organism [postulates 1 and 2] proves a causal relationship
Does HIV Fulfill Koch’s Postulates?

- Virus isolated from all patients with AIDS
- Cell culture models and knowledge of virus life cycle support hypothesis
- No adequate animal model but SIV and SHIV in rhesus macaques produce AIDS-like illnesses
- Transfusion cases, needle stick acquisitions come closest to human model of infection and disease

Adults and Children Estimated to be Living with HIV in 2007

Total: 33.2 (30.6–36.1) million
Hantavirus Pulmonary Syndrome

New Agent and Disease

Hantavirus Pulmonary Syndrome: First Description

- Rapidly fatal illnesses with respiratory failure reported initially in a couple, ages 21 and 19, living in rural New Mexico reported on May 14, 1993
- Cluster of cases reported from Four Corners area
  - New Mexico, Arizona, Colorado, Utah
- New agent – Sin Nombre Virus identified
  - A hantavirus
- Rodent host identified
  - Deer mouse
- Cases outside of Four Corners area reported

Hantaviruses

- Members of the family Bunyaviridae
- Segmented RNA, enveloped viruses
- Two basic syndromes
  - Hemorrhagic fever with renal syndrome (HFRS)
  - Hantavirus pulmonary syndrome (HPS)
- Reservoirs in nature
  - Chronically infected rodents of the family Muridae
  - Subfamilies
    - Murinae (Old World rodents) are reservoirs for Hantaan, Dobrava and Seoul viruses (HFRS causing)
    - Arvicolinae (voles) are reservoirs for Puumala virus and Prospect Hill virus (HFRS causing)
    - Sigmodontinae (New World rats and mice) are the reservoirs for Sin Nombre virus (HPS causing)

Transmission of Hantaviruses

- Chronically infected rodent
- Horizontal transmission of infection by intraspecies aggressive behavior
- Virus is present in aerosolized excreta, particularly urine
- Virus also present in throat and feces
- Secondary aerosols, mucous membrane contact, and skin breaches are also a consideration
Rodent Reservoir of Sin Nombre Virus

*Peromyscus maniculatus*
Deer mouse

Hantavirus Pulmonary Syndrome: Pathogenesis

- Inhalation of particle contaminated with infectious virus
  - Deposition in terminal respiratory bronchiole or alveolus
- Local replication with viremia
- Widespread infection of pulmonary endothelium
  - Cell invasion may be mediated by B3 integrins
- Infiltration by CD4 and CD8 cells
- Loss of vascular integrity in lungs
- Capillary leak syndrome
- Myocardial depression also seen
Hantavirus Pulmonary Syndrome:
Clinical Findings

- Onset 14-17 days after exposure
- Myalgia, malaise and fever
- Anorexia, nausea, vomiting and abdominal pain may ensue
- Cough, tachypnea and tachycardia
- Rapid progression to respiratory failure
- Laboratory
  - Hemoconcentration (elevated Hct)
  - Leukocytosis with left shift; atypical lymphocytes also seen
  - Thrombocytopenia
  - Elevated liver enzymes, proteinuria, elevated creatinine may be seen
  - Interstitial edema on chest film → air space disease and pleural effusions

Hantavirus Pulmonary Syndrome
Radiographic Findings

- Bilateral interstitial infiltrates
  - moderate to rapid progression
- Bilateral alveolar infiltrates
- Pleural effusion
Avian Influenza

Known Disease in New Host

• Only influenza A infects birds
  – H5, H7 and H9 most common
    • Potentially 9 different subtypes for each (N1-N9)
    • H5 and H7 can vary in pathogenicity
    • H9 typically low in pathogenicity
• Transmission to humans
  – Directly from birds or contaminated environment
  – Via an intermediate host – e.g., pig
• Human cases reported since 1997
Avian Influenza in Humans: History

- 1997: H5N1 – Hong Kong
- 1999: H9N2 – China and Hong Kong
- 2002: H7N2 – Shenandoah Valley, VA
- 2003: H5N1 – China and Hong Kong
- 2003: H7N7 – Netherlands
- 2003: H9N2 – Hong Kong
- 2003: H7N2 – New York
- **2004: H5N1** – Thailand and Vietnam → Ongoing
- 2004: H7N3 – Canada

Avian Influenza: Cumulative Human Cases
12/26/03 – 7/1/09

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam</td>
<td>111</td>
<td>56</td>
</tr>
<tr>
<td>Thailand</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Indonesia</td>
<td>141</td>
<td>115</td>
</tr>
<tr>
<td>Cambodia</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Myanmar</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>China</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Egypt</td>
<td>81</td>
<td>27</td>
</tr>
<tr>
<td>Turkey</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Pakistan</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Iraq</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Nigeria</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Djibouti</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>436</strong></td>
<td><strong>262</strong></td>
</tr>
</tbody>
</table>

Source: www.who.int
Avian Influenza H5N1 in 2004

- Poultry outbreaks in 8 countries in Asia
  - 100 million birds died or culled
- Human cases
  - 17 cases and 12 deaths in Thailand
  - 27 cases with 20 deaths in Vietnam
  - One human-to-human case reported
- Movement into other species
  - Pigs in China; tigers and leopards in Vietnam
- Antiviral and vaccine possibilities
  - Resistant to amantadine and rimantadine
  - Generally sensitive to zanamivir and oseltamivir
    - Oseltamivir resistance in H5N1 strains reported, however
  - Vaccine under development
- The big question: Is a global pandemic on the horizon?

Generation of a Potentially Pandemic Strain of Influenza through Reassortment

H5N1 Avian Influenza in Poultry and Wild Birds Since 2003

Data thru 9/27/07

H5N1 Avian Influenza in Humans Since 2003

Data thru 5/6/09
Avian Influenza: Challenges to Control

Variant Creutzfeldt-Jakob Disease (vCJD) (Bovine Spongiform Encephalopathy)

Known Disease in a New Form

Science 2004;306:392-399
Prions

- Proteinaceous infectious particles
- NOT viruses
- Responsible for the transmissible spongiform encephalopathies (TSE's)
  - Pathologic hallmark
    - Spongiform changes in brain
    - Absence of inflammation

Kuru

Papua New Guinea
### Clinical features of Kuru

<table>
<thead>
<tr>
<th>Transmission</th>
<th>Autoinoculation/ingestion of infected brain material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>Fore linguistic group of Papua New Guinea</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Cerebellar ataxia, tremor, movement disorders</td>
</tr>
<tr>
<td></td>
<td>Mental impairment, emotional lability,</td>
</tr>
<tr>
<td></td>
<td>frontal release signs (snout, suck, root, grasp</td>
</tr>
<tr>
<td></td>
<td>reflexes)</td>
</tr>
<tr>
<td>Course</td>
<td>Fatal 9-24 months after onset</td>
</tr>
</tbody>
</table>
Spongiform Encephalopathy - Histology

Normal section

Kuru

Linking Kuru to an Infectious Agent (Gajdusek)

Kuru

Brain

Fungus

Chimpanzee

Kuru-like disease
## Prion Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Natural Host</th>
<th>Prion</th>
<th>Pathogenic PrP Isoform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrapie</td>
<td>Sheep and goats</td>
<td>Scrapie Prion</td>
<td>PrP^Sc</td>
</tr>
<tr>
<td>Transmissible mink encephalopathy (TME)</td>
<td>Mink</td>
<td>TME Prion</td>
<td>PrP^Tm</td>
</tr>
<tr>
<td>Chronic wasting disease (CWD)</td>
<td>Deer and elk</td>
<td>CWD Prion</td>
<td>PrP^Cw</td>
</tr>
<tr>
<td>Bovine spongiform encephalopathy (BSE)</td>
<td>Cattle</td>
<td>BSE Prion</td>
<td>PrP^Bo</td>
</tr>
<tr>
<td>Feline spongiform encephalopathy (FSE)</td>
<td>Cats</td>
<td>FSE Prion</td>
<td>PrP^Fe</td>
</tr>
<tr>
<td>Exotic ungulate encephalopathy (EUE)</td>
<td>Nyla &amp; greater kudu</td>
<td>EUE Prion</td>
<td>PrP^Eu</td>
</tr>
</tbody>
</table>

## Spongiform Encephalopathies

- BSE
- CJD

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Center for Animal Health and Productivity - U. Penn
Human Prion Diseases

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>SYMPTOMS</th>
<th>ACQUISITION</th>
<th>DISTRIBUTION</th>
<th>DISEASE COURSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuru</td>
<td>Loss of coordination followed by dementia</td>
<td>Infection (transmission)</td>
<td>200 cases identified in Papua New Guinea</td>
<td>3 mo - 1 yr</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob Disease</td>
<td>Dementia followed by loss of coordination</td>
<td>Usually unknowable (sporadic)</td>
<td>Sporadic: 1 in 1,000,000</td>
<td>Usually 1 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15% of cases involve an inherited mutation in the PRNP gene</td>
<td>Inherited: 100 extended families identified</td>
<td>but as short as 1 mo and as long as 10 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rabies infection through contaminated surgical instrument or organ transplant</td>
<td>Infectious: 80 cases identified</td>
<td></td>
</tr>
<tr>
<td>Gerstmann-Sträussler-Scheinker Disease</td>
<td>Loss of coordination followed by dementia</td>
<td>Inheritance of a mutation in the PRNP gene</td>
<td>Sporadic: 50 extended families identified</td>
<td>2-4 yrs</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>Trouble sleeping and disturbance of the autonomic nervous system, behavioral changes, dementia and loss of coordination</td>
<td>Inheritance of a mutation in the PRNP gene</td>
<td>9 extended families identified</td>
<td>About 1 yr</td>
</tr>
</tbody>
</table>

Creutzfeldt-Jakob Disease

- Most common human TSE - about 1 case/million/yr
- Three forms traditionally recognized
  1. sCJD - sporadic, about 85% of cases
  2. tCJD - familial, about 10% of cases
  3. iCJD - iatrogenic, about 5% of cases
- In 1996 a new variant emerged in the U.K. - vCJD
  - Associated with eating beef infected with BSE agent (Mad Cow)
  - In contrast with traditional forms of CJD, vCJD strikes young adults
  - Crosses species barrier
BSE Epidemic in UK

Search for the Agent (Prusiner Lab)

- Extremely small, proteinaceous infectious particle
- Resistant to DNAse and RNAse
- Resistant to limited proteolysis
- Resistant to chemical agents that inactivate conventional viruses
Genetic mutations in CJD and other Prion Diseases

Prion Disease

- External source
  - Ingestion
  - Iatrogenic
    - Organ transplant
    - Contaminated surgical instruments

- Sporadic

- Inheritance of a defective gene

Presenile conformational conversion

- Plaque deposition

- Deposited in CNS

- PrP protein

- Cellular PrP protein

- Signal Sequence

- PrPc
How Does Conformational Conversion Occur?

Soluble → Increase in β-strand content → Insoluble

Introduction of infectious pathogenic form (Scrapie, BSE)

Heritable mutations that promote spontaneous conversion (CJD)

Prion Disease - Amyloid Deposition

Normal form
Solute

Disease form
Insoluble

α-helical form

β-strands

Protein-protein interaction

Conformational transition

Growing plaque deposit

Prior protein bundles

fibrillary astrocytosis
Normal PrP<sup>C</sup> Required for Disease Progression

**PrP Gene Knockout**
- Not susceptible to prion disease
- Possibly more prone to seizures

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**What is Normal PrP<sup>C</sup>?**

- Glycoprotein ~250 amino acids
- Membrane associated through a C-terminal glycosphatidylinositol (GPI) linkage
- Role in membrane trafficking has been proposed - possibly involved in some endocytic pathways
- Knockout mice develop and behave normally, but perhaps prone to seizures
- Interacts with laminin, which plays a role in cell adhesion and neurite formation
- Also interacts with the laminin receptor resulting in internalization of membrane-bound PrP<sup>C</sup>
- Binds Cu<sup>2+</sup> - may have an antioxidant function that promotes neuron survival
- Abundant in brain - also detected in: spleen, lymph node, lung, heart, kidney, skeletal muscle, uterus, adrenal gland, parotid gland, intestine, and mammary gland.
Current View of Prion Disease Development

- Prions ingested and absorbed by intestines (Peyers Patches)
- Gains access to lymphoid fluids and blood
- Deposited in lymphoid tissues where it amplifies through conformational conversion
- Amplified prions deposited in brain - perhaps crosses blood-brain barrier or migrates by axonal transport
- Replicates in brain - toxicity resulting in neuronal cell death

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Classic CJD</th>
<th>Variant CJD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at death</td>
<td>68 years</td>
<td>28 years</td>
</tr>
<tr>
<td>Median duration of illness</td>
<td>4-5 months</td>
<td>13-14 months</td>
</tr>
<tr>
<td>Clinical signs and symptoms</td>
<td>Dementia;</td>
<td>Prominent psychiatric/behavioral symptoms; painful dyesthesias; delayed neurologic signs</td>
</tr>
<tr>
<td></td>
<td>early neuro signs</td>
<td>Often present; Not reported; Rare or absent; Variable accumulation</td>
</tr>
<tr>
<td>’Brien’s sharp waves on electroencephalogram</td>
<td>Often present</td>
<td>Marked accumulation of protease-resistance prion protein; Readily detected</td>
</tr>
<tr>
<td>&quot;Pulvinar sign&quot; on MRI</td>
<td>Not reported</td>
<td>Marked accumulation of protease-resistance prion protein</td>
</tr>
<tr>
<td>Presence of &quot;florid plaques&quot; on neuropathology</td>
<td>Rare or absent</td>
<td>Present in large numbers</td>
</tr>
<tr>
<td>Immunohistochemical analysis of brain tissue</td>
<td>Variable accumulation</td>
<td>Marked accumulation of protease-resistance prion protein</td>
</tr>
<tr>
<td>Presence of agent in lymphoid tissue</td>
<td>Not readily detected</td>
<td>Readily detected</td>
</tr>
<tr>
<td>Increased glycoform ratio on immunoblot analysis of protease-resistance prion protein</td>
<td>Not reported</td>
<td>Marked accumulation of protease-resistance prion protein</td>
</tr>
</tbody>
</table>

www.cdc.gov
Emerging Infectious Diseases

- **AIDS worldwide**
  - 5 cases → ~60 million cases with ~25 million deaths in 28 years

- **Hantavirus Pulmonary Syndrome**
  - 465 laboratory confirmed cases reported in the U.S. since 1993 from 30 states; majority in Southwest; 35% mortality

- **Avian influenza**
  - 436 cases with 262 deaths 12/26/03-7/1/09
  - What’s next?
    - ??Pandemic with 10-100 million deaths??

- **vCJD**
  - 200 cases from 1996 – 2007
    - 164 in UK, 21 in France, 4 in Ireland, 3 in the U.S., 2 in the Netherlands and 1 each in Canada, Italy, Japan, Portugal, Saudi Arabia and Spain
    - What’s next?

Emerging Infectious Diseases: Website Resources

- [www.cdc.gov](http://www.cdc.gov)
- [www.idssociety.org](http://www.idssociety.org)
- [www.promedmail.org](http://www.promedmail.org)